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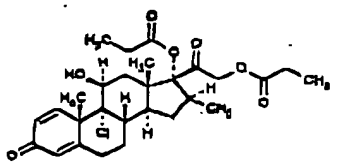
Beclomethasone Dipropionate



$C_{28}H_{37}ClO_7$ 521.05
Pregna-1,4-diene-3,20-dione, 9-chloro-11-hydroxy-16-methyl-17,21-bis(1-oxopropoxy)-, (11β,16β)-.
9-Chloro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate [5534-09-8].
Monohydrate 539.07.

» Beclomethasone Dipropionate is anhydrous or contains one molecule of water of hydration. It contains not less than 97.0 percent and not more than 103.0 percent of $C_{28}H_{37}ClO_7$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed containers.

USP Reference standards ⟨11⟩—*USP Beclomethasone Dipropionate RS. USP Testosterone Propionate RS.*

Identification, *Infrared Absorption* ⟨197M⟩.

Specific rotation ⟨781S⟩: between +88° and +94°.
Test solution: 10 mg per mL, in dioxane.

Loss on drying ⟨731⟩—Dry it at 105° for 3 hours: the anhydrous form loses not more than 0.5% of its weight; the monohydrate form loses between 2.8% and 3.8% of its weight.

Residue on ignition ⟨281⟩: not more than 0.1%.

Assay—
Mobile solvent—Prepare a suitable degassed solution of 3 volumes of acetonitrile in 2 volumes of water, such that the retention time of beclomethasone dipropionate is approximately 6 minutes and that of testosterone propionate is approximately 10 minutes.
Internal standard solution—Dissolve a suitable quantity of USP Testosterone Propionate RS, accurately weighed, in methanol to obtain a solution having a concentration of about 1.2 mg per mL.
Standard preparation—Dissolve a suitable quantity of USP Beclomethasone Dipropionate RS, accurately weighed, in methanol to obtain a solution having a concentration of about 1.4 mg per mL. Transfer 4.0 mL of this solution to a suitable vial, and add 4.0 mL of *Internal standard solution*, to obtain a solution having a known concentration of about 0.7 mg per mL with respect to the Reference Standard and 0.6 mg per mL with respect to the internal standard.
Assay preparation—Weigh accurately about 70 mg of Beclomethasone Dipropionate, transfer to a 50-mL volumetric flask, dilute with methanol to volume, and mix. Transfer 4.0 mL of this solution to a suitable vial, and add 4.0 mL of *Internal standard solution*.
Procedure—Introduce equal volumes (between 5 µL and 25 µL) of the *Assay preparation* and the *Standard preparation* into a high-performance liquid chromatograph (see *Chromatography* ⟨621⟩) operated at room temperature, by means of a suitable microsyringe or sampling valve, adjusting the specimen size and other operating parameters such that the peak obtained with the internal standard in the *Standard preparation* is about 0.6 to 0.9 full-scale. Typically, the apparatus is fitted with a 4-mm × 30-cm column packed with packing L1 and is equipped with an ultraviolet detector capable of monitoring absorption at 254 nm, a suitable recorder, and a pump capable of operating at a column pressure of up to 3500 psi. In a suitable chromatogram, the coefficient of variation for five replicate injections of the *Standard preparation* is not more than 3.0%. Calculate the quantity, in mg, of $C_{28}H_{37}ClO_7$ in the portion of Beclomethasone Dipropionate taken by the formula:

$$100C(R_U/R_S),$$

in which C is the concentration, in mg per mL, of USP Beclomethasone Dipropionate RS in the *Standard preparation*, and R_U and R_S are the peak height ratios of beclomethasone dipropionate to the internal standard, at equivalent retention times, obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Belladonna Extract

» Belladonna Extract contains, in each 100 g, not less than 1.15 g and not more than 1.35 g of the alkaloids of belladonna leaf.

Pilular Belladonna Extract

Prepare the extract by percolating 1000 g of Belladonna Leaf, using a mixture of 3 volumes of alcohol and 1 volume of water as the menstruum. Macerate the drug for 16 hours, and then percolate it at a moderate rate. Evaporate the percolate under reduced pressure and at a temperature not exceeding 60° to a pilular consistency, and adjust the remaining extract, after assaying, by dilution with liquid glucose so that the finished Extract will contain, in each 100 g, 1.25 g of the alkaloids of belladonna leaf.

Powdered Belladonna Extract

Prepare the extract by percolating 1000 g of Belladonna Leaf, using alcohol as the menstruum. Macerate the drug for 16 hours, and then percolate it slowly. Evaporate the percolate under reduced pressure and at a temperature not exceeding 60° to a soft extract, add 50 g of dry starch, and continue the evaporation, at the same temperature, until the product is dry. Powder the residue. The extract may be deprived of its fat by treating either the soft extract first obtained, or the dry and powdered extract, as directed under *Extracts* ⟨see *Pharmaceutical Dosage Forms* ⟨1151⟩⟩. Assay the powdered residue, and add sufficient starch, previously dried at 100°, to obtain a finished Extract containing 1.25 g of the alkaloids of belladonna leaf in each 100 g. Mix the powders, and pass the Extract through a fine sieve.

Packaging and storage—Preserve in tight containers, at a temperature not exceeding 30°.

USP Reference standards ⟨11⟩—*USP Atropine Sulfate RS. USP Homatropine Hydrobromide RS. USP Scopolamine Hydrobromide RS.*

Assay—
pH 9.5 phosphate buffer—Dissolve 34.8 g of dibasic potassium phosphate in 900 mL of water, and adjust to a pH of 9.5, determined electrometrically, by the addition of 3 *N* hydrochloric acid or sodium hydroxide, with mixing.
Internal standard solution—Dissolve about 40 mg of USP Homatropine Hydrobromide RS, accurately weighed, in about 25 mL of dilute sulfuric acid (1 in 350) in a 50-mL volumetric flask, add the same dilute acid to volume, and mix. Prepare fresh on the day of use.
Standard preparation—Dissolve about 10 mg of USP Scopolamine Hydrobromide RS, accurately weighed, in about 5 mL of dilute sulfuric acid (1 in 350), in a 10-mL volumetric flask, add the same dilute acid to volume, and mix (*Solution A*). Dissolve about 20 mg of USP Atropine Sulfate RS, accurately

weighed, in about 25 mL of dilute sulfuric acid (1 in 350) in a 50-mL volumetric flask, add 2.0 mL of *Solution A*, and mix. Add dilute sulfuric acid (1 in 350) to volume, and mix. Prepare fresh on the day of use.

Extraction blank—Place about 10 mL of dilute sulfuric acid (1 in 350) in a 60-mL separator. Proceed as directed under *Assay preparation*, beginning with "then add 15 mL of chloroform." The blank chromatogram contains no significant interferences at the locus of atropine, scopolamine, or homatropine.

Assay preparation—Weigh accurately about 0.5 g of Extract, transfer to a 125-mL conical flask, and add 40 mL of dilute sulfuric acid (1 in 350). Heat to a temperature not above 45°, and stir to hasten solution. Filter the solution through filter paper into a 100-mL volumetric flask. Wash the flask and the filter with two 20-mL portions of warmed dilute sulfuric acid (1 in 350), and collect the washings in the 100-mL volumetric flask. Add dilute sulfuric acid (1 in 350) to volume, and mix.

Pipet 10 mL of this solution into a 60-mL separator. To the separator add 1.0 mL of *Internal standard solution*, then add 15 mL of chloroform, shake vigorously, allow the layers to separate, and discard the chloroform layer. (If emulsions are formed, a *mixed solvent* consisting of chloroform and isopropyl alcohol (10:3) may be substituted for chloroform throughout the extraction procedure.) Add another 15 mL of chloroform, and extract again, discarding the chloroform phase. Add 15 mL of *pH 9.5 phosphate buffer* and sufficient 1 *N* sodium hydroxide to yield a final pH between 9.0 and 9.5. Add 15 mL of chloroform, shake vigorously, and allow the layers to separate. Filter the organic phase through 10 g of anhydrous sodium sulfate (see *Suitability for alkaloid assays* under *Sodium Sulfate, Anhydrous*, in the section *Reagents, Indicators, and Solutions*), previously washed with chloroform and supported in a funnel with a small pledget of glass wool, into a suitable container. Extract again with two 15-mL portions of chloroform, again collecting the clarified organic phase. Wash the sodium sulfate and the tip of the funnel with 5 mL of chloroform. Evaporate the combined organic phases under reduced pressure, at a temperature below 45°, add 1 mL of chloroform, and mix to dissolve the alkaloids, taking care to wet the sides of the container.

Standard curve—Prepare three *Standard solutions* as follows: Pipet into three separate 60-mL separators 1.0-, 2.0-, and 3.0-mL portions, respectively, of *Standard preparation*, and add 9.0, 8.0, and 7.0 mL, respectively, of dilute sulfuric acid (1 in 350). Proceed as directed under *Assay preparation*, beginning with "add 1.0 mL of *Internal standard solution*."

Chromatographic system—Under typical condition, the instrument contains a 1.2-m × 4-mm glass column packed with 3 percent G3 on S1AB. The column may be cured and conditioned as specified under *Gas Chromatography* (see *Chromatography* (621)). The column is maintained at a temperature of about 215°, and the injection port and detector block at about 240°, and dry helium is used as a carrier gas at a flow rate of about 65 mL per minute.

System suitability—Chromatograph six to ten injections of the solution, and record peak areas as directed under *Procedure*. The analytical system is suitable for conducting this assay if the relative standard deviation for the ratio, R_A, calculated by the formula:

$$100 \times (\text{standard deviation/mean ratio}),$$

does not exceed 2.0%; the resolution, R, between a_H and a_A is not less than 3; and the tailing factor (the sum of the distances from peak center to the leading edge and to the tailing edge divided by twice the distance from peak center to the leading edge), measured at 5% of the peak height of a_A, does not exceed 2.0.

Procedure—Inject a portion (about 5 µL) of each *Standard solution* into a suitable gas chromatograph equipped with a flame-ionization detector. Measure the areas, a_A, a_H, and a_S, of the atropine, homatropine, and scopolamine peaks, respectively, in each chromatogram, and calculate the ratios A_A and A_S by the formulas:

$$a_A/a_H \text{ and } a_S/a_H.$$

Plot the *Standard curves* of the values of R_A and R_S against the amounts, in mg, of atropine and scopolamine in the solutions. (The ratio of the molecular weight of atropine to that of anhydrous atropine sulfate is 0.8551, and the ratio of the molecular weight of scopolamine to that of anhydrous scopolamine hydrobromide is 0.7894.) Inject a portion of the *Assay preparation* into the chromatograph, obtain the chromatogram area ratios, measure the peak areas, and calculate the area ratios, as with the *Standard solutions*. Record from the *Standard curve* the quantities, in mg, of atropine and scopolamine in the volume of specimen taken. Add the quantity, in mg, of atropine and scopolamine, and multiply by 10 to obtain the weight, in mg, of alkaloids in the portion of Extract taken.

Belladonna Extract Tablets

» Belladonna Extract Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of the alkaloids of belladonna leaf.

Packaging and storage—Preserve in tight, light-resistant containers.

USP Reference standards (11)—*USP Atropine Sulfate RS*. *USP Homatropine Hydrobromide RS*. *USP Scopolamine Hydrobromide RS*.

Identification—Macerate a quantity of powdered Tablets, equivalent to about 5 mg of the alkaloids of belladonna extract, with 20 mL of water, and transfer to a separator. Render the solution alkaline with 6 *N* ammonium hydroxide, and extract the alkaloids with 50 mL of chloroform. Filter the chloroform layer, divide it into two equal portions, and evaporate to dryness: the residue responds to the following tests.

A: To one portion of the dry residue add 2 drops of nitric acid, evaporate on a steam bath to dryness, and add a few drops of alcoholic potassium hydroxide TS: a violet color is produced.

B: Dissolve the other portion of the residue in 1 mL of dilute hydrochloric acid (1 in 120), and add gold chloride TS, dropwise with shaking, until a definite precipitate separates. Slowly heat until the precipitate dissolves, and allow the solution to cool: a lusterless precipitate is produced.

Disintegration (701): 30 minutes.

Uniformity of dosage units (905): meet the requirements.

Assay—

Internal standard solution, *Standard preparation*, *Extraction blank*, *Standard curve*, *Chromatographic system*, and *System suitability*—Proceed as directed in the *Assay* under *Belladonna Extract*.

Assay preparation—Weigh and finely powder not less than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 600 µg of atropine and scopolamine, to a 60-mL separator, add 10.0 mL of dilute sulfuric acid (1 in 350), and sonicate to dissolve as much as possible of the specimen. Proceed as directed for *Assay preparation* in the *Assay* under *Belladonna Leaf*, beginning with "add 1.0 mL of *Internal standard solution*."

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Belladonna Extract*. Record from the *Standard curves* the quantities, in mg, of atropine and scopolamine in the weight of specimen taken.

Belladonna Leaf

» Belladonna Leaf consists of the dried leaf and flowering or fruiting top of *Atropa belladonna* Linné or of its variety *acuminata* Royle ex Lindley (Fam. Solanaceae). Belladonna Leaf yields not less than 0.35 percent of the alkaloids of belladonna leaf.